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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,083	03/06/2002	David McCallister	EFFR0010U-US	8537

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/092,083	MCCALLISTER ET AL.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,55-58 and 61-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53, 55-58, 61-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 7/21/08.

Claims 1-52, 54, 59-60 have been cancelled. Claims 53, 55-58, 61-63 are pending.

Claims 53, 56, 58 have been amended. Claims 53, 55-58, 61-63 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejection of the last Office Action is maintained for reasons of record and modified or repeated below for Applicant's convenience.

The following new rejection will now apply.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 53 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 25, 39-42 of

copending Application No. 11/473044. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite a method of treating osteoporosis in a mammal by administering a composition comprising a bisphosphonate, an acid component, an alkaline effervescing component, and an anti-ulcer agent. It is obvious to select alendronate because it is a well known species of the genus, bisphosphonate.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 53, 55-58, 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katdare et al. (US Patent 5,853,759) in view of Daifotis et al. (US Patent 5,994,329).

Katdare et al. discloses that bisphosphonates including instant preferred bisphosphonates such as alendronate are known to have utility as pharmaceutical agents for inhibiting bone resorption (see col. 1, lines 14-42). Katdare et al. particularly discloses that a composition comprising the instantly preferred bisphosphonate and alendronate, can be orally administered and is known to be useful in a method of treating osteoporosis in postmenopausal women (human mammals) (see col.1, lines 43-49). The disclosed pharmaceutical effervescent formulations of alendronate therein in tablet, which are placed in an convenient amount of water to produce effervescent liquid (solution), and that the patient drinks the effervescent solution, are for eliminating or minimizing side effects during the medication (i.e., for treating osteoporosis and/or inhibiting bone resorption in a mammal) (see col.1, lines 8-1 1 and 48-57, col.2 lines 63-67). The particular disclosed alendronate effervescent compositions of Katdare et al. in Example 1-4 comprises alendronate in an effective amount (known for treating osteoporosis and/or inhibiting bone resorption), the instant preferred acid component, citric acid, and the instant preferred alkaline effervescing component, sodium bicarbonate and sodium carbonate, flavoring agent or sweetener and color agent, and then an convenient amount of water added to produce effervescent solution to be administered orally (see Example 1 at col.4 line 34-35 and 46-56 in particular), and the

composition also comprises a lubricant such as sodium benzonate and polyethylene glycol (PEQ) (also known as a solubilizing agent (see col.2 lines 24-26 and col.4 lines 21-33).

Note that the total weight of the solid composition of Katdare et al. in claims 4-5 therein is 3.365 g (see claims 4-5, adding up the weight of all solid ingredients). Moreover, the total weight of the table is known to range from about 100 to about 50,000 mg, about 1500-32500 mg, or about 20,800-30,150 mg (see col.3, lines 1-5).

The weight percentage of the acid component in Example 1 is 58.7 wt % (which is calculated by 650 mg of citric acid per 1106.5 mg of total weight, see Example 1 at col.4), which is substantially close to about 45 wt % of the instant claimed range. The amount of bisphosphonate such as alendronate in the prior art composition ranges from 1 to 80 mg, overlapping with the instant claim.

Generally, mere optimization of ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also *In re Peterson*, 315 F. 3d at 1330, 65 USPQ 2d at 1382 "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." MPEP 2114.04.

It has been held that it is within the skills in the art to select optimal parameters,

such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See In re Boesch, 205 USPQ 215 (CCPA 1980).

Regarding the inherent property, the pH of the solution, it is noted that citric acid is employed in an excess in the composition therein to efficiently generate the effervescence and to sequester any ions to complex with alendronate, and to enhance flavor as well, disclosed by Katdare et al. (see col.3 lines 60-65). Thus, the solution therein is acidic. The pKa of citric acid (known to used as a buffer), pK1, K2, K3 are 3.128, 4.761, and 6.396, respectively (provided by Bull "An Introduction to Physical Biochemistry" page 103, PTO-892). Thus, one of ordinary skill in the art would clearly recognize that the pH values in citric acid buffered solutions would be within the instantly claimed range about 3 to about 6.5, as shown in the calculation below:

Example I discloses that citric acid is 650 mg and the molecular weight (or formula weight, FW) of citric acid is 192.12 (provided by Aldrich Handbook page 436, PTO-892).

Thus, the moles of citric acid is 650 ÷ 192.12 = 3.38 mmol.

Example I discloses that sodium bicarbonate is 367 mg and the molecular weight of sodium bicarbonate is 84.01 (provided by Aldrich Handbook page 1505, PTO-892).

Thus, the moles of sodium bicarbonate is 367 ÷ 84.01= 4.37 mmol.

Example I discloses that sodium carbonate is 40 mg and the molecular weight of sodium carbonate is 105.99 (provided Aldrich Handbook page 1498, PTO-892). Thus, the moles of sodium carbonate is 40 + 105.99 =0.38 mmol.

It is known in the basic chemistry that the mole ratio of citric acid carbonate for neutralizing citric acid by sodium carbonate (or known as equal equivalent) is 2:3 (see col.3 line 67 to col.4 line 1) and the mole ratio of citric acid to sodium bicarbonate for neutralizing citric acid by sodium bicarbonate is 1:3.

Thus, 4.37 mmol of sodium bicarbonate neutralizes 4.87 X 1/3 = 1.46 mmol of citric acid; 2.65 mmol of sodium carbonate neutralizes 0.38 X 2/3 = 0.25 mmol of citric acid; Therefore, the left or excess of citric acid in the solution = 3.38 - (1 .46 + 0.25) =1.67 mmol.

Therefore, 1.67 mmol, about a half amount of citric acid is free and left in the solution. Thus, the solution is acidic. As discussed above, according the known pKa values of citric acid, the pH value of the effervescent composition of Example 1 could be within the instant claim.

Moreover, after administering of the effervescent solution of Katdare et al., the pH of the mammal's stomach would be inherently raised to the range here since the citric acid solution is a known buffered solution which would mediate the pH in the mammal's stomach for a period of time of 15 minutes or more.

"Products of identical chemical composition can not have mutual exclusive properties." Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to the applicant to show that the prior art product does not inherently possess the same properties as the instantly claimed product.

Katdare et al. does not expressly disclose an anti-ulcer agent.

Daifotis et al. teach that treating abnormal bone resorption, particularly osteoporosis (col. 1, lines 29-31), by oral administration of alendronate, a potent bisphosphonate compound (col. 1, lines 54-55). Despite their therapeutic benefits, bisphosphonates are poorly absorbed from the gastrointestinal tract (col. 2, lines 3-5), thus oral administration has been associated with adverse gastrointestinal effects, such as esophageal ulcers (col. 2, lines 23-30). As a result, Daifotis et al. discloses bisphosphonate compositions that also comprise histamine H2 receptor blockers (H_2-antagonists) and proton pump inhibitors, such as cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole, which are the instant preferred anti-ulcer agents, in order to minimize adverse gastrointestinal effects produced by bisphosphonates (see col.13 lines 19-46).

It would have been obvious to a person of ordinary skill in the art at the time the

invention was made to combine the anti-ulcer agents disclosed by Daifotis et al. in the composition comprising bisphosphonates disclose by Katdare et al. for the treatment of osteoporosis.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine the anti-ulcer agents disclosed by Daifotis et al. in the composition disclose by Katdare et al. for the treatment of osteoporosis because: (1) both Katdare and Daifotis et al. are analogous are since both teach the treatment of osteoporosis by orally administration of a composition comprising bisphosphonates; (2) Daifotis et al. teach that bisphosphonates are poorly absorbed from the gastrointestinal tract which lead to adverse gastrointestinal effects, such as esophageal ulcers; (3) Daifotis et al. teach that anti-ulcer agents such as cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole, can be used to minimize such adverse gastrointestinal effects produced by bisphosphonates. Therefore, the skilled artisan would have had a reasonable expectation of success in treating osteoporosis with a composition comprising bisphosphonates, while at the same time minimizing the adverse gastrointestinal effects produced by bisphosphonates with the addition of anti-ulcer agents.

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... The idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Response to Arguments

The Rohrich Declaration under 37 CFR 1.132 filed 5/30/08 is insufficient to overcome the 103(a) obviousness rejection. Applicant attempts to show nonobviousness by comparing the pH values of the instant invention and the four examples in the Katdare reference and example 8 in the Daifotis reference. This is not persuasive because Applicant is reminded that this is a 103 obviousness rejection based on a combination of references and not a 102 rejection based on a single reference. It has been stated that it is obvious to optimize the pH of the composition taught by the cited prior art. Examiner does not know why then the exact same compositions in the examples were measured. Nonetheless, Katdare's examples show a pH at the lower limit of the claimed range as well as at the upper limit. This is not a showing of unexpected or surprising results.

Furthermore, arguments directed to example 8 of Daifotis, not being effervescent is not persuasive because the rejection is based on a combination of references, where Katdare teach an effervescent composition.

In response to applicant's arguments against the references, one cannot show nonobviousness by attacking references individually where the rejections are based on the combination of references. See *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant is reminded that the instant claims are drawn to a method of treating osteoporosis by administering a composition comprising a bisphosphonate and an anti-

ulcer agent. There are no limitations in the instant claims regarding the effect of enhanced absorption of bisphosphonate.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The Hayward Declaration #1 under 37 CFR 1.132 filed 5/30/08 is insufficient to overcome the 103(a) obviousness rejection because the Declaration is not commensurate with the scope of the claims. Specifically, EX101 contains 70 mg of alendronate, whereas the instant claims do not recite an amount range for alendronate. Also, the Declaration does not compare EX101 with the closest prior art, but rather with commercial 70 mg Fosamax tablets from Merck & Co. as submitted to the FDA as part of a New Drug Application. Finally, going from 82% to 57% in coefficient of variation for the drug absorption of EX101 is not considered surprising or unexpected.

The Hayward Declaration #2 under 37 CFR 1.132 filed 5/30/08 is insufficient to overcome the 103(a) obviousness rejection because the Declaration does not present any unexpected results but rather states various clinical observations on patients being administered the claimed composition.

The Hayward Declaration #3 under 37 CFR 1.132 filed 7/21/08 is insufficient to overcome the 103(a) obviousness rejection because the Declaration compares the instant composition with that of Fosamax tablets again in terms of gastric emptying

times. Again, this Declaration does not compare with the closest prior art. Also, the claims are drawn to a method of treating osteoporosis and not to improving alendronate tolerability.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Regarding the establishment of unexpected results or synergism, a few notable principles are well settled. The Applicant has the initial burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). It is applicant's burden to present clear and convincing factual evidence of nonobviousness or unexpected results, i.e., side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art. The claims must be commensurate in the scope with any evidence of unexpected results. See MPEP 716.02 (d). With regard to synergism, a prima facie case of synergism has not been established if the data or result is not obvious. The synergism should be sufficient to overcome the obviousness, but must also be commensurate with the scope of the claims. Further, if the Applicant provides a DECLARATION UNDER 37 CFR 1.132, it must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case if obviousness. See MPEP 716.02 (e).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Yong S Chong/
Examiner, Art Unit 1617

YSC